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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/031,918	09/24/2002	Joseph P. Noel	SALK2370-2	1639

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FOLEY & LARDNER LLP
P.O. BOX 80278
SAN DIEGO, CA 92138-0278

EXAMINER

NASHED, NASHAAT T

ART UNIT	PAPER NUMBER
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1656

DATE MAILED: 11/15/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/031,918	NOEL ET AL.	
	Examiner	Art Unit	
	Nashaat T. Nashed, Ph. D.	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on 29 September 2005.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-39 is/are pending in the application.
- 4a) Of the above claim(s) 1-5,7-16,18-21 and 27-39 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 6, 17, and 22-26 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

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The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1656.

The application has been amended as requested in the communication files September 29, 2005. Accordingly, claims 1 and 22 have been amended.

Claim 1 as currently amended is no longer reading on selected Group I, which is directed to polyketide synthase and crystal thereof. Claim 1, as currently amendment, reads on a three-dimensional model of a polyketide synthase. As indicated in the previous Office action, mailed May 25, 2005, the special technical feature of elected invention of Group I is the polyketide synthase, which was previously known in the prior art, and not the contribution of the applicants. While the crystal of and the polyketide synthase itself are two form of said polyketide synthase, and not directly related to the three dimensional structure. Said structure is a product of a method using the crystal to determine the structure of said synthase by the X-ray diffraction method. Thus, claim 1 as amended has been withdrawn from further consideration by the examiner because it is not directed to polyketide synthase or crystal thereof.

Applicants affirm their election of Group I, and the election of naringenchalcone-synthase from *medicago sativa* (alfalfa) in their of September 28, 2005. They traverse the restriction of Group III-V on the ground that they have the same technical feature. Applicants arguments filed September 29, 2005 have been fully considered, but they are found unpersuasive. The amended claim 1 special technical feature is the atomic coordinates, which is the special technical feature for the methods of inventions III-V. Had the embodiments of claim 1 as amended presented in the original claims, claims 1 and 12-16 would have defined as an invention because the applicants are entitled to the special technical feature and a single method of its use and/or making, see 37 CFR 1.475(b)(3). Other methods of use of the same technical feature define new invention. The traversal of the restriction requirement of Groups III-V is moot because none of inventions III-V are elected for examination in this application filed under 35 USC 371.

Also, applicants traversed the restriction requirement on the ground that the identity of the side chains does not make any difference since the position of the alpha-carbon atoms are the same and define the claimed invention. The claimed invention is directed to a genus of polyketide synthase having different structure and function. They are independent chemical compounds and require different searches in the patent and non-patent literature. Moore importantly, they are not obvious variant from one another. Thus, the restriction requirement is proper and therefore, is made final.

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37

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CFR 1.821 through 1.825. The atomic coordinates in Table 3 represents the disclosure of an amino acid sequence, which has to be identified by a sequence identification number. Also, Table 1 contains a list of amino acid residues, which has to be identified by amino acid identification number. Through out the specification, there are many cited specific amino acid residues, which are not associated with a sequence identification number, see for example Table 1, and pages 178-180, 185, and 192. Also, new Tables 5-8 at page 6 of the amendment filed September 29, 2005 constitute an amino acid sequence discloser and should be identified by a sequence identification number. Applicants must perfect their compliance with the sequence rules.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17, and 22-26 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the reasons set forth in the prior Office action, mailed May 25, 2005.

Applicants argue that claim 1 is directed to a three-dimensional representation of a specific polyketide synthase, and methods of mutagenesis, expression, purification, crystallization, data collection, structure determination, model building,etc. are provided in the specification and therefore, the claims are fully described.

Applicants arguments filed 9/29/05 have been fully considered, but they are found unpersuasive. Claim 1 as amended is no longer read on the elected subject matter of elected Group I, i.e., a polyketide synthase, and therefore, withdrawn from further consideration. Claims 17, and 22-26 are drawn to a crystal of a chalcon synthase and remain under consideration. The examiner agrees that methods of mutagenesis, purification, data collection, model building and refinement are known in the prior art. The instant claims are directed to genus of crystals of chalcone synthase defined by the atomic coordinates of 14 alpha-carbon atoms. The specification, however, describe the crystallization of two members of the genus. The specification failed to describe other members of this genus by any other characteristic other than the atomic coordinated of the 14 alpha-carbon atoms, let alone the crystallization conditions that produces a single crystal suitable for structure determination by the X-ray diffraction method.

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Claims 17, and 22-26 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement for the reasons set forth in the prior Office action, mailed May 25, 2005.

Applicants argue that this rejection is based on erroneous analysis of the wand factors.

Applicants arguments filed 9/29/05 have been fully considered, but they are found unpersuasive. Enablement requires a disclosure sufficient to allow a person of skill in the art to practice the full scope of the claimed invention without undue experimentation. The previous Office action sets out a *prima facie* case of non-enablement, explaining by sound scientific reasoning why a person of ordinary skill in the art would doubt that the guidance of the specification would enable practice of the full scope of the claimed invention without undue experimentation. Applicants have presented no evidence or, indeed, any arguments to establish the adequacy of the disclosure to enable the scope of the instant claims. Applicants merely assert that the rejection is based on erroneous analysis of the wand factors without submitting any evidence or reasonable scientific arguments. Applicants make no effort to explain why they consider the disclosure of two crystals of two chalcone synthase are enabling disclosure for all possible crystals of chalcone synthase having specific atomic coordinates of 14 alpha-carbon atoms. Conclusory statements unsupported by evidence or scientific reasoning are insufficient to overcome the *prima facie* case of non-enablement set out in the previous Office action.

The following is response to applicants' argument in the order of their appearance in the response filed 9/29/05:

- (1) The examiner has not incorrectly characterized the invention. The examiner interpreted the claim as broadly as it can be reasonably interpreted. The subject matter of claim 1 as amended has been changed and no longer under consideration. Claims 17 and 22-26 are directed to a crystal of just about any chalcone synthase. Applicant should be reminded that there is no relationship between the structure of a protein and the condition under which a suitable crystal for X-ray determination can be obtained. A single amino acid change may have a profound effect on a protein ability to be crystallized.
- (2) It may be true that applicants are the first to obtain an X-ray crystallographic structure of polyketide synthase such as chalcone synthase. It is not clear to this examiner why the applicants are entitled to any crystallized polyketide synthase such as chalcone synthase as well as type I polyketide synthases.

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- (3) While the relative skill of those in the art is high, there is some aspect of structure determination of protein remain highly unpredictable, see item (4) bellow.
- (4) Applicants argue that the predictability in the X-ray crystallography was increased significantly with respect to polyketide synthase. Indeed, applicant has made a positive contribution to the art. The art of determining the structure a protein by single crystal diffraction method remains as it has been since the first protein crystal diffraction of X-ray in the 1930's. The method is dependent on obtaining an adequate single crystal that diffracts X-ray and produce sufficient amount of data to produce the structure. While many aspect of the technology made easier and faster by the development of computers and modeling software, recombinant methods to obtain sufficient amount of the desired protein to screen for crystallization conditions, protein purification methods, and even kits to screen for the appropriate crystallization conditions. Methods of obtaining protein crystal, however, rely on screening methods to obtain crystals suitable for the diffraction method. There are many variables including changing the amino acid sequence of a protein and crystallization in microgravity environment, i.e., crystallization in space. While an ordinary skill in the art knows what to do to obtain a crystal, obtaining a crystal remains a trial and error and there is no methodical approach to obtain a crystal. Thus, an ordinary skill in the art has to try many approaches to crystallization of the protein without expectation of obtaining a crystal. Finally, when a crystal is obtained, it may or may not be suitable for structure determination by X-ray. Thus, growing crystals requires a large amount of work from a highly skilled artisan without any expectation of success. Applicants have not explained why obtaining a crystal of a specific mutant chalcone synthase and a specific 2-pyrone synthase is sufficient disclosure enabling any crystal for any polyketide synthase. Claims directed to the specific embodiment of the two crystals with a sequence identification number would overcome this rejection.
- (5) Claim 1 is no longer under consideration. Applicant has made no arguments regarding the scope of claims 17 and 22-26.
- (6) The only claim amended substantively is claim 1, which is no longer under consideration. With regard to claims 17 and 22-26, the teaching of he specification is commensurate with the scope of the claimed invention.
- (7 & 8) As indicated above, the previous Office action sets out a *prima facie* case of non-enablement, explaining by sound scientific reasoning why a person of ordinary skill in the art would doubt that the guidance of the specification would enable practice of the full scope of the claimed

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invention without undue experimentation. Applicants have failed to rebut the *prima facie* case of lack of enablement.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 6, 17, 22, and 26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following are the reasons for the rejections:

- (a) The phrase "the polyketide synthase of claim 1" in claims 6 and 17 are confusing and indefinite, because the resulting claim does not set forth the metes and bounds of the claimed invention. Claim 6 and 17 are directed to polyketid synthase and are dependent on claim 1 which is directed to three-dimensional representation of the polyketide synthase. For examination purposes only, the claims are assumed to be drawn to polyketide synthase, which include all the embodiment of original claim 1.
- (b) The phrases "PDB Accession Nos: 1BI5" in claim 6 renders the claims indefinite because the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. The phrase remains confusing because one of ordinary skill in the art would not know what it means. The substitution of "PDB Accession Nos: 1BI5" with Table 5 would obviate this rejection. Although applicant introduced new Table 5 to the specification containing the atomic coordinates to the specificatio, applicants must refer to Table 5 and identifying the amino acid sequence correspond to that in the Table by a sequence identification number.
- (c) The result in Tables 1 contains amino acid residues from a specific amino acid sequence not identified by a sequence identification number, which renders claims 6 and 17 indefinite and confusing. For examination purposes only, it is assumed that the applicant is referring to residues from SEQ ID NO: 1. In response to this rejection, applicants argue that it is clear from the specification that the amino acid residues in Table 1 are from SEQ ID NO: 1. Applicants' arguments have been fully considered, but they are found unpersuasive. Applicant should reevaluate the requirement of rule 37 CFR 1.821(d), which require the amino acid sequence identification number to follow the mentioning the protein at each occurrence.

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- (d) The clause "the chalcone synthase is selected from the group consisting of chalcone....." in claim 26 renders the claims indefinite because the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. An enzyme named chalcone synthase should produce chalcone as a product. Thus, chalcone, naringenin, resveratrol and cerulenin can be possibly a substrate for a chalcone synthase. For examination purposes only, the substrate for chalcone synthase is malonylCoA. In response to this rejection, applicants argue that it is well known in the art of enzymology and enzyme nomenclature that the name ascribed to an enzyme does not necessarily reflect the direction of chemical reaction or even the reactants involved in the reactions. Applicants' arguments have been fully considered, but they are found unpersuasive. The directionality of a reaction catalyzed by any catalyst including enzymes is determined by the equilibrium position of the reaction and not by the enzyme itself. In fact, the enzyme catalyzes both forward and reverse reaction with the same efficiency. As for naming the enzymes, the applicants' assertions that enzymes are not named after their substrate is simply erroneous. Also, the examiner recognizes that fact that enzymes may act on more than one substrate, but those other substrates are not their biological substrates and should be identified as such.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 6 is rejected under 35 U.S.C. 102(a) as being anticipated by Protein Data Bank Accession number 1BI5 (IDS reference, released to the public June 22, 1999) for the reasons set forth in the prior Office action, mailed May 25, 2005.

In response to the above rejections, applicants argue that PDB 1BI5 is applicants own work, Dixon did not contribute to the present invention, and that applicants are prepared to file *in re Katz* declaration. In addition, they argue that Austin is not an inventor of the instant claims and they are intended to remove his name from this application.

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Applicants arguments filed 9/29/05 have been fully considered, but they are found unpersuasive. When applicant file the required declaration and remove Austin as a co-inventor from the application, the rejection will remain on the record.

Claim 6 is rejected under 35 U.S.C. 102(b) as being anticipated by Junghans *et al.* (IDS reference, Plant Mol. Biol. 22, 239-253, 1993) for the reasons set forth in the prior Office action, mailed May 25, 2005.

Applicants argue that claim 1, presumably, as amended requires a three-dimensional representation, which distinguish the claimed polyketide synthase from that of the prior art.

Applicants arguments filed 9/29/05 have been fully considered, but they are found unpersuasive. Claim 1 as amended is no longer read on the elected subject matter of elected Group I, i.e., a polyketide synthase, and therefore, withdrawn from further consideration. If claim 6 is drawn to a polyketide synthase having a particular three-dimensional representation, the claim remains rejected because the structure of the protein is an intrinsic property of a known polyketide synthase. Identifying a new property of a known chemical compound does not render the chemical compound novel. Thus, the claimed invention remain rejected until the applicants distinguish there claimed polyketide synthase from that of the prior art. If claim 6 is correctly dependent from claim 1 as currently amended, the claim would be withdrawn from further consideration because it would be directed to non-elected subject matter.

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).


A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nashaat T. Nashed, Ph. D. whose telephone number is 571-272-0934. The examiner can normally be reached on MTWTF.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr, Ph. D. can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).


Nashaat T. Nashed, Ph. D.
Primary Examiner
Art Unit 1652